Remarks

Claims 11 and 16 have been amended. Support for the amendments can be found at paragraphs [0003], [0005] and Fig. 2 of the published application which teaches the compound naltrindole (NTI) of Formula I which is a δ-opioid receptor antagonist. The Applicants believe the amendments place the claims in better condition for allowance, or alternatively in better condition for appeal. Entry of the amendments is respectfully requested.

At the outset, the Applicants would like to thank the Examiner for the interview of August 11, 2008, summarize here the topics discussed during the interview, and address these topics in this Response. The discussion of the fact that Rudd and the other references teach only treatment of emesis induced by nicotine through the nicotinic acetyl choline receptors, but not treatment of emesis induced by μ-opioid receptor agonists was very helpful and has been incorporated into the arguments in this Response. Those aspects of the cited references that teach away from the claimed methods, show unpredicatibility, and which show that one of ordinary skill in the art would not be motivated to perform the claimed methods were also discussed. Additionally, the failure of the references to teach all the elements of the claimed methods was discussed. These topics are addressed below.

Claims 11-12, 14 and 16 are rejected under 35 USC §103(a) over the combination of US '680 (Portoghese), Rudd, Neeleman and Meijer. The rejection states that US '680 teaches a compound within the genus of compounds used in the claimed methods. The rejection states that US '680 teaches that morphine causes vomiting in some individuals. The rejection also states that US '680 teaches administering compounds of the claims to treat vomiting induced by the μ-opioid agonist morphine. The rejection further states that Rudd teaches the compound natrindole (NTI) which is identical to that of the compounds of the claimed methods. The rejection states that Rudd also teaches NTI can be used to treat vomiting caused by the μ-opioid receptor agonist fentanyl. The

rejection states that Neeleman teaches morphine is a μ-opioid receptor agonist. Elsewhere the rejection states Sosis teaches the μ-opioid agonist fentanyl causes vomiting. The rejection then concludes that the claimed methods are obvious over this combination.

Amended Claims 11-12, 14 and 16 are not obvious under 35 USC §103(a) over the combination of US '680, Rudd, Neeleman, Meijer and Sosis. Independent Claim 11 has been amended to recite "administering a therapeutically effective amount of an δ-opioid receptor antagonist agent comprising a morphinan derivative represented by general formula (I)" and specify the functional properties of the compounds useful in the claimed methods. Claims 12, 14 and 16 are dependent on independent Claim 11 and incorporate all of its limitations. First, different pharmacological effects are mediated by the various opioid receptors, and these effects are specific to each receptor type. *See* Goodman & Gilman, The Pharmacological Basis of Therapeutics, pg. 525, Table 23-3 (1996). For example, all μ-, δ-, and κ-opioid receptor agonists exert analgesic effects, but only κ-opioid receptor agonists produce psychotomimetic and diuretic effects. Therefore, all that US '680 teaches is that μ-opioid receptor agonists can be analgesic drugs, which produce none of the side effects of κ-opioid receptor agonists such as psychotomimesis or diuresis.

Importantly, US '680 does not teach that nausea and vomiting, which are side effects of μ-opioid receptor agonists such as morphine, can be treated by δ-opioid receptor antagonists such as naltrindole (NTI). *See also* Goodman & Gilman, The Pharmacological Basis of Therapeutics, pg. 524, Table 23-2 (1996) (concerning μ-opioid receptor agonist side effects). Furthermore, it is known that naltrexone and naloxone, which are μ-opioid receptor antagonists, can prevent the nausea and vomiting that are side effects of morphine administration, because such μ-opioid receptor antagonists can antagonize all the effects of the μ-opioid receptor agonist morphine.

Moreover, the Applicants note that such μ-opioid receptor antagonists are not useful as part of a drug combination for the treatment, or prevention, of nausea or vomiting caused by the systematic administration of morphine. *See e.g.* paragraph [0003] of the published application. This is because μ-opioid receptor antagonists also impair the analgesic effect of morphine. *See* 65(16) Life Science 1685-1695 (1999).

The Applicants have unexpectedly discovered that naltrindole (NTI), which is a δ-opioid receptor antagonist and similar δ-opioid receptor antagonist compounds, can selectively treat nausea and vomiting caused by the μ-opioid receptor agonist morphine without suppressing the analgesic effect of morphine.

Second, the relation between opioids (especially μ-opioid receptor agonists) and vomiting is complex. This is because μ-opioid receptor agonists induce nausea and vomiting when administered in small doses, but suppress nausea and vomiting when administered in large doses. *See* 30 Neuropharmacology 1073-1083 (1991). Importantly, Rudd focuses on the suppression of nicotine induced nausea and vomiting by the administration of a large amount of the μ-opioid receptor agonist fentanyl and reports the mechanism for suppressing nausea and vomiting induced by nicotine. *See* Rudd, abstract, lines 1-3.

Rudd used receptor antagonization experiments employing different opioid receptor antagonists to determine that the anti-emetic effects of the μ-opioid receptor agonist fentanyl is mediated by μ_2-opioid receptors and that naltrindole (NTI) or similar δ-opioid receptor antagonists do not alter the anti-emetic effect produced by administering large amounts of fentanyl. *See* Rudd, abstract, lines 5-6. These findings mean that Rudd does not teach or suggest the anti-emetic effect of δ-opioid receptor antagonists to control nausea and vomiting caused by the administration of μ-opioid receptor agonists.

Third, Rudd also mentions that administration of large doses of the μ-opioid receptor antagonists naloxone or naltrexone induce nausea and vomiting. *See* Rudd at 77, abstract, lines 7-8. However, this information from Rudd is irrelevant to the rejected claims. This is because the purpose of the claimed subject matter is to treat nausea and vomiting caused by the administration of a small dose of a μ-opioid receptor agonist.

The foregoing makes it clear that a person of ordinary skill in the art would not use naltrindole (NTI) or similar δ-opioid receptor antagonists in combination with a μ-opioid receptor agonist to suppressing nausea and vomiting mediated by the μ-opioid receptor despite the teachings in US '680 and Rudd. Instead, one skilled in the art might merely be motivated to use selective opioid agonists as analgesic drugs free of some of the side effects caused by other types of opioid receptors or to use the μ-opioid receptor agonist fentanyl to treating nausea and vomiting induced by nicotine and mediated though nicotine acetyl choline receptors.

Amended Claims 11-12, 14 and 16 are also not obvious under 35 USC §103(a) over the combination of US '680, Rudd, Neeleman, Meijer and Sosis in light of the following additional arguments.

First, amended Claims 11-12, 14 and 16 are not obvious because this combination of references fails to teach all the elements of the claimed methods. US '680, for example, simply does not teach treating nausea and vomiting caused by μ-opioid agonist compounds such as morphine. Rudd also does not teach the administration of NTI, or other structurally similar δ-opioid receptor antagonists, for the treatment of nausea and vomiting caused by a μ-opioid agonist compound such as morphine. Instead, Rudd merely teaches that nicotine induced emesis can be treated by the μ-opioid receptor agonist fentanyl. As seen in Table 2 of Rudd, NTI (abbreviated there as "NALT") by itself has no effect on nicotine induced emesis and does not reverse the anti-emetic effects of

fentanyl. Together this means that the combination of US '680, Rudd, Neeleman, Meijer and Sosis fails to teach all the elements of the claimed methods, such as the treatment of nausea and vomiting induced by μ-opioid agonists induced by μ-opioid agonists. Importantly, Neeleman, Meijer and Sosis fail to correct this deficiency of the core combination of US' 680 and Rudd.

Second, amended Claims 11-12, 14 and 16 are not obvious because one skilled in the art would not be motivated to combine these references to perform the claimed methods of treatment. At the outset, it is important to note that nicotine mediates its biological effects through nicotinic acetylcholine receptors. This means the emesis induced by nicotine in Rudd is mediated by these nicotinic acetyl choline receptors not through the stimulation of μ-opioid receptors by μ-opioid receptor agonist such as morphine or fentanyl. In other words, Rudd merely shows that the μ-opioid receptor agonist fentanyl prevents nicotine induced emesis.

This is significant for three reasons, each of which shows that one skilled in the art would not be motivated to combine Rudd with the other references cited to perform the claimed methods of treatment. The first reason there is no motivation to combine Rudd and the other cited references is that Rudd is concerned with emesis that is dependent on an entirely different set of receptors than the μ-opioid receptors. This means Rudd's study of emesis induced by the μ-opioid receptor antagonists naltrexone, naloxone, and naloxone methylbromide is irrelevant to the claimed methods in which the administration of δ-opioid receptor antagonists, such as NTI, is used to treat nausea and vomiting caused by μ-opioid receptor agonists, such as morphine.

The second reason there is no motivation to combine Rudd and the other cited references is that Rudd shows the μ-opioid receptor agonist fentanyl is an anti-emetic compound, while the δ-opioid receptor antagonist NTI by itself is entirely ineffective in preventing emesis. *See e.g.* Rudd at 79 (Table 1). In fact, Rudd states their data show "that the anti-emetic mechanism is likely to

involve μ- but not δ- or κ-opioid receptors." *See* Rudd at 83 (emphasis added). The Applicants respectfully submit that all the teachings of the prior art should be considered especially those teachings in Rudd and the other references which clearly teach away from using δ-opioid receptor antagonists to control emesis.

The discussion above demonstrates that Rudd would not motivate one skilled in the art to use a δ-opioid receptor antagonist, such as NTI, to treat nausea and vomiting caused by a μ-opioid receptor agonist compound, such as morphine. This is particularly true because NTI is a δ-opioid receptor antagonist, and as such would not be expected to antagonize the μ-opioid receptors that mediate morphine induced vomiting. However, there is more.

The third reason there is no motivation to combine Rudd and the other cited references is that Sosis states that "[t]he multifactorial aspects of emesis makes...studies particularly difficult to control and this is amply demonstrated by the literature." This means that one skilled in the art would not be motivated to attempt to combine the teachings of different, poorly controlled studies intended to examine emesis associated with the administration of such widely different drug treatments as nicotine in Rudd; nitrous oxide/oxygen/fentanyl or enflurane/nitrous oxide/ oxygen as discussed in Sosis; and droperidol, nitrous oxide and oxgen as discussed in Sosis. This lack of appropriate controls (*e.g.* for the different drugs combinations; model animals, patient groups *etc.*) between the various studies cited in the rejection would mean that one skilled in the art would conclude that any combination of the teachings of these references would produce highly unpredictable results. In fact, the comments in Sosis alone show that even those skilled in the art believe it is debatable whether the μ-opioid agonist fentanyl by itself actually even causes emesis. Consequently, one skilled in the art would not reasonably expect to successfully combine the teachings of these references to perform the claimed methods. Stated differently, one skilled in the

art would have no motivation to pick and choose the different, discrete aspects of the references cited in the rejection or to successfully combine these references as suggested in the rejection.

In light of the foregoing, the Applicants respectfully request withdrawal of the rejections of amended Claims 11-12, 14 and 16 under 35 USC §103(a) and allowance of these claims.

Last, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

T. Daniel Christenbury
Reg. No. 31,750
Attorney for Applicants

TDC/vbm
(215) 656-3381